REMARKS/ARGUMENTS

Upon entry of the present amendment, claims 1, 2, 6, 9, 11, 12, 15, 18, 19, 21, 22, 25, 28, 30-34, 36, 37, 40, 43, 45-48, 51, 54, 180, and 182-186 are pending in this application.

Claims 1, 11, 21, 31, 45, 180 and 204-209 have been amended to more clearly define the invention.

The present amendment does not introduce new matter.

Claim Objections

As requested by the Examiner to place the claims in better form, Applicants have amended claims 1, 11, 21, 31, 45, 180 and 204-209 to insert the word "a" before "beta-cyclodextrin". Therefore, Applicants respectfully request withdrawal of the present objection.

Rejection under 35 U.S.C. §103(a)

Claims 1, 2, 6, 9, 11, 12, 15, 18, 19, 21, 22, 25, 28, 30-34, 36, 37, 40, 43, 45-48, 51, 54, 180, 182-186 and 204-209 are rejected under 35 U.S.C. §103(a) as being unpatentable over WO 00/61142 to Pardee ("Pardee"), taken in view of U.S. Patent No. 4,983,586 to Bodor ("Bodor").

It is well recognized under U.S. law, that any rejection of a claim for obviousness over a combination of prior art references must establish that: (1) the combination produces the claimed invention; and (2) the prior art contains a suggestion or motivation to combine the prior art references in such a way as to achieve the claimed invention. *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). The motivation to modify the prior art must flow from some teaching in the art that suggests the desirability or incentive to make the modification needed to arrive at the claimed invention. *In re Napier*, 34 U.S.P.Q.2d 1782, 1784 (Fed. Cir. 1995). The mere fact that the prior art could be modified does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Laskowski*, 10 U.S.P.Q.2d 1397, 1399 (Fed. Cir. 1989).

The Examiner states that the primary reference, Pardee, discloses the use of β-lapachone or analogs and derivatives thereof in combination with G2/M phase drugs, such as taxol, to treat cancer. The Examiner also states that Pardee discloses dosage ranges, kits, various methods of administration and that β-lapachone is insoluble in water. However, the Examiner states that Pardee does not disclose using a beta-cyclodextrin as a solubilizing agent. *See*, Office Action at page 3. The Examiner completes the rejection by stating that the secondary reference Bodor teaches that

hydroxypropyl-beta-cyclodextrin is useful for solubilizing a wide variety of water-insoluble drugs, particularly anti-neoplastic/anti-tumor agents, by complexation but that Bodor does not disclose β-lapachone or analogs or derivatives thereof. *See*, Office Action at pages 3-4. The Examiner asserts that it would have been obvious to have solubilized the anti-neoplastic/anti-tumor agents of the primary reference (β-lapachone and taxol) by complexing them with hydroxypropyl-beta-cyclodextrin to improve solubility for parenteral administration and that determining the suitability of a given drug for complexation with hydroxypropyl-beta-cyclodextrin is merely a matter of routine. *See*, Office Action at page 4. Applicants traverse.

Applicants submit that there is no suggestion or motivation to combine Pardee and Bodor to reach the present invention. The ordinary skilled artisan reading Pardee would not be motivated to improve on the solubility of the disclosed anti-cancer agents, β-lapachone or taxol. As stated by the Examiner, Pardee is directed to the combination of these agents in treating cancer in a synergistic manner. In fact, in teaching the combination of these agents to treat cancer, Pardee discloses that the inventors have been successful in solubilizing the water-insoluble β-lapachone compound and the partially water soluble taxol compound using the formulating agent, lipiodol (*See*, page 21, lines 8-10 and lines 16-18) and that these lipiodol formulated compounds of β-lapachone and taxol can be administered intraperitoneally or intravenously. *See*, page 21, lines 20-21. Specifically, Pardee teaches "β-lapachone was formulated into solution using lipiodol, a medium agent used clinically. **Our success with this formulating agent (lipiodol) solved the long standing problem of insolubility of β-lapachone.**" **(Emphasis Added)**. *See*, page 21, lines 8-10. Pardee also teaches an alternative formulation for solubilizing β-lapachone in cremphor plus ethanol. *See*, page 21, lines 12-14. Further, the working examples of Pardee teach the successful use of β-lapachone and taxol formulated in lipiodol to treat cancer (inhibition of tumor growth, lessening tumors, reducing tumor angiogenesis, *etc.*) *in vivo* by administering these β-lapachone/lipiodol and taxol/lipiodol formulations to mice. *See* page 21, line 7 – page 24, line 8; Figures 2-7. Pardee teaches the formulations showed no toxicity. *See*, page 22, line 14 and line 33. *See*, Reddy Declaration ¶ 7.

Since Pardee teaches the solubilization of β-lapachone and taxol in lipiodol and the utility of these formulations in treating cancer without toxic side-effects, the skilled artisan reading Pardee would have no desire or incentive to make a modification to arrive at the claimed invention (*i.e.* a pharmaceutical composition comprising a therapeutically effective amount of β-lapachone

solubilized by beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin). The mere fact Pardee could be modified (*i.e.* that β-lapachone or taxol could be solublized by different solubilizing agents/carriers) does not make the modification obvious. Thus, one of ordinary skill in the art reading Pardee would not be motivated to combine the teachings of Pardee with the teachings of Bodor to reach the present invention. *See*, Reddy Declaration ¶ 7.

Applicants submit that the Examiner has improperly applied hindsight in combining Pardee and Bodor in reaching the present obviousness rejection. Determination of obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention. *Crown Operations Int'l, LTD v. Solutia Inc.*, 289 F.3d 1367 (Fed. Cir. 2002). In making the assessment of differences, 35 U.S.C. § 103 specifically requires consideration of the claimed invention "as a whole." Inventions typically are new combinations of existing principles or features (noting that "virtually all [inventions] are combinations of old elements."). *Envtl. Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693 (Fed. Cir. 1983). The "as a whole" instruction in 35 U.S.C. § 103 prevents evaluation of the invention part by part. *Ruiz v. A.B. Chance Co.*, 357 F.3d 1270 (Fed. Cir. 2004). Without this important requirement, an obviousness assessment might break an invention into its component parts (A + B + C), then find a prior art reference containing A, another containing B, and another containing C, and on that basis alone declare the invention obvious. *Id.* This form of hindsight reasoning, using the invention as a roadmap to find its prior art components, would discount the value of combining various existing features or principles in a new way to achieve a new result - often the very definition of invention. *Id.* Thus, there must be a teaching or suggestion within the prior art, within the nature of the problem to be solved, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources, to select particular elements, and to combine them as combined by the inventor. *Id.* When the patented invention is made by combining known components to achieve a new system, the prior art must provide a suggestion or motivation to make such a combination. *Id.* Therefore, as discussed *supra*, Applicants submit that the combination of Pardee and Bodor do not contain a suggestion or motivation to combine them in such a way to achieve the claimed invention.

Reasonable Expectation of Success:

Further, Applicants submit that the standard applied to Pardee and Bodor by the Examiner is not a *prima facie* case of obviousness standard (*See*, MPEP § 2143). A proper obviousness analysis requires consideration of "whether the prior art would also have revealed that in so making or carrying out [the claimed invention], those of ordinary skill would have a reasonable expectation of success." *In re Vaeck*, 947 F.2d at 493. Further, "The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art." *In re Dow Chemical Co.*, 837 F.2d 469 (Fed. Cir. 1988).

The reasonable expectation of success requirement has two distinct components. First, the guidance that the reference provides must be sufficiently specific to direct the attention to one skilled in the art to the selection of parameters and choices necessary to obtain the invention. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). Prior art does not satisfy this requirement if it is necessary to vary all parameters, or to try each of numerous possible choices, in order possibly to arrive at successful results. *Id.* The second and related element of a reasonable expectation of success is that the prior art suggesting the desirability of the invention must enable one of ordinary skill in the art to produce it. *Id.*

Applicants submit that there is no expectation of success combining Pardee and Bodor to reach the present invention. One of ordinary skill in the art would not reasonably expect the β-lapachone or analogs or derivatives or taxol compounds disclosed in Pardee to be successfully combined with the general beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin disclosure of Bodor to produce a water-soluble pharmaceutical composition comprising β-lapachone that is therapeutically effective.

Bodor does not disclose the use of beta-cyclodextrin for solubilizing β-lapachone or any other compounds but rather Bodor merely discloses the contemplated use of a modified beta-cyclodextrin, hydroxypropyl-beta-cyclodextrin, to solubilize a very broad family of lipophilic or water-insoluble drugs/compounds and a broad genus of anti-neoplastics (anti-cancer/anti-tumor agents). *See*, Col. 14, line 51 – Col. 15, line 47. In fact, Bodor teaches away from the use of beta-cyclodextrin as a solubilizing agent for water-insoluble or water-poorly soluble drugs/compounds (*i.e.* β-lapachone, taxol, *etc.*) based on the lack of solubility of beta-cyclodextrin. Specifically, Bodor states "β-cyclodextrin has been of special interest because of its cavity size, but its relatively

low aqueous solubility has limited its use in the pharmaceutical field." *See*, Col. 2, lines 7-10. *See*, Reddy Declaration ¶ 8.

With respect to the solubility of anti-neoplastic agents with hydroxypropyl-beta-cyclodextrin, of the myriad of water-insoluble, anti-neoplastic compounds known in the art, Bodor only discloses nineteen contemplated compounds. *See*, Col. 15, lines 5-10. Further, Bodor only discloses working examples for solubilizing Methotexate, Chlorambucil, Lomustine and Melphalan in hydroxypropyl-beta-cyclodextrin. *See*, Col. 76, lines 44-49; Col. 77, Table III; Col. 76, line 65 – Col. 79, line 44 including Tables V – VIII. *See*, Reddy Declaration ¶ 9.

One of ordinary skill in the art reading the general disclosure of Bodor with the limited number of anti-neoplastic compounds disclosed would not combine that disclosures with the disclosure of Pardee to reach the present invention with a reasonable expectation of success. There are many water-insoluble, antineoplastic compounds (*e.g.* taxol (paclitaxel), etoposide, vincristine, vinblastine, cisplatin, staurosporin, UCN-01, *etc.*) that are not readily solubilized with beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin. Specifically, taxol, an anti-neoplastic as disclosed in Pardee, is not rendered soluble in beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin. Further, Bodor discloses that etoposide is a contemplated water-insoluble anti-neoplastic compound which can be solubilized with hydroxypropyl-beta-cyclodextrin. In fact, etoposide, a topoisomerase poison disclosed in Pardee, is not rendered soluble in beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin as suggested by Bodor. *See*, Reddy Declaration ¶ 9.

The ability of beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin to solubilize water-insoluble or poorly water-soluble drugs/compounds depends on the ability of the drug/compound to fit into the cavity of the cyclodextrin ring system. Thus, factors such as size and charge can preclude the introduction of a drug/compound into the cavity of beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin due to steric hindrance contraints. As described, Bodor only discloses nineteen contemplated anti-neoplastic compounds that could be solublized in hydroxypropyl-beta-cyclodextrin. The chemical structures of some of the disclosed anti-neoplastic compounds are disclosed in Bodor. *See*, Col. 46 and 57-60. One of ordinary skill in the art reading Bodor would readily recognize that these disclosed chemical structures are much smaller in size when compared to the chemical structures of the β-lapachone or analogs or derivatives or taxol compounds disclosed in Pardee and that while the Bodor compounds may fit into the cavity of beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin the larger compounds of Pardee would not readily fit into the

cavity. Also, as discussed above, taxol is known not to be rendered soluble in beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin with reasonable quantities and is not stable upon dilution with water or saline that are necessary for parenteral administration. *See*, Reddy Declaration ¶ 10.

Since Bodor only generally discloses anti-neoplastic compounds which are contemplated to be solubilized by hydroxypropyl-beta-cyclodextrin and these contemplated compounds are much different in chemical structure (*i.e.* smaller in size, differing ring structures) from the chemical structure of β-lapachone or its analogs and derivatives and the chemical structures of many anti-neoplastic compounds, most notably taxol and etoposide, which as described are not readily soluble in beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin, Bodor does not provide sufficient, specific guidance to one of ordinary skill in the art to select the specific parameters and choices necessary to reach the present invention. Therefore, Applicants submit that one of ordinary skill in the art would have no reasonable expectation of success combining the teachings of Pardee and Bodor to reach the presently claimed invention. *See*, Reddy Declaration ¶ 10.

Unexpected Results:

Moreover, a determination of whether the claimed subject matter as a whole would have been obvious at the time the invention was made involves factual findings with respect to secondary considerations, including unexpected results. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). Applicants submit that one of ordinary skill in the art would not have expected a pharmaceutical composition comprising β-lapachone solubilized by beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin to be therapeutically effective.

The present invention discloses that combining, mixing, and/or complexing β-lapachone with hydroxypropyl-beta-cyclodextrin increases the aqueous solubility of β-lapachone, improves the stability of β-lapachone to photoreduction, and shows that the solubility of β-lapachone increases linearly with the increase in hydroxypropyl-beta-cyclodextrin concentration. *See*, specification at page 8, lines 8-12; Table 2; page 9, lines 5-11; page 21, line 5 – page 23, line 7; page 24, line 6 – page 25, line 7; Figures 1-2. As described *supra*, Bodor only discloses nineteen anti-neoplastic/anti-tumor agents contemplated for parenteral formulation with hydroxypropyl-beta-cyclodextrin. *See*, Col. 15, lines 5-10. Moreover, Bodor only discloses working examples for the solubility of Methotexate, Chlorambucil, Lomustine and Melphalan in hydroxypropyl-beta-cyclodextrin. *See*, Col. 76, lines 44-49; Col. 77, Table III; Col. 76, line 65 – Col. 79, line 44 including Tables V – VIII.

Specifically, in describing the solubility of these compounds Bodor discloses that when Chlorambucil, Lomustine and Melphalan are complexed with hydroxypropyl-beta-cyclodextrin to increase solubility, degradation of the drug occurred and in the case of Chlorambucil, significant degradation occurred. *See*, Col. 78, lines 30-49. *See*, Reddy Declaration ¶ 11.

As the specification demonstrates, the present invention teaches that when β-lapachone is combined, mixed, or complexed with hydroxypropyl-beta-cyclodextrin, β-lapachone shows significantly better stability in the dark at 5 days and 21 days and also when exposed to normal room brightness at room temperature. *See*, page 24, line 6 – page 25, line 7. Specifically, this teaching is critical for producing a pharmaceutical composition comprising a therapeutically effective amount of β-lapachone since the administration and use of the pharmaceutical composition depends upon the ability of the drug of interest (*i.e.* β-lapachone or analogs and derivatives thereof) to be administered and delivered to a particular target (*i.e.* a cancer cell). To do so effectively, the drug of interest must be soluble and stable (not readily degradable) and remain soluble and stable prior to administration (*e.g.* parenteral). The results described in the specification demonstrate that the claimed invention displays the surprising, unexpected and superior stability of a pharmaceutical composition comprising a therapeutically effective amount of β-lapachone solubilized by beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin. These results were not taught or suggested by either Pardee or Bodor alone or in combination. Therefore, the combination of Pardee and Bodor could not lead the ordinarily skilled artisan to the unexpected and superior advantages (increased stability of β-lapachone) that the claimed invention provides. *See*, Reddy Declaration ¶ 11.

The § 103 rejection should be withdrawn.

CONCLUSION

In view of the aforementioned remarks and amendments, the Applicants believe that each of pending claims is in condition for allowance. Reconsideration, withdrawal of the rejections, and passage of the case to issue is respectfully requested. A notice to this effect is earnestly solicited.

If, upon receipt and review of this amendment, the Examiner believes that the present application is not in condition for allowance and that changes can be suggested which would place the claims in allowable form, the Examiner is respectfully requested to call Applicant's undersigned counsel at the number provided below.

Respectfully submitted,

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